The ACEF (age, creatinine, ejection fraction) score predicts ischemic and bleeding outcomes of patients with acute coronary syndromes treated conservatively

Artur Dziewierz[1], Zbigniew Siudak[2], Tomasz Rakowski[1], Wojciech Zasada[1], Katarzyna Krzanowska[3], Dariusz Dudek[2]

[1]2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Interventional Cardiology, Jagiellonian University Medical College, Krakow, Poland
[3]Chair and Department of Nephrology, Jagiellonian University Medical College, Krakow, Poland

Adv Interv Cardiol 2017; 13, 2 (48): 160–164
DOI: https://doi.org/10.5114/pwki.2017.68209

Introduction

Assessment of both ischemic and bleeding risk is crucial for the management of patients with coronary artery disease, especially patients with acute coronary syndromes (ACS) [1, 2]. At present, the use of the Global Registry for Acute Coronary Events (GRACE) risk score is recommended in patients presenting with non-ST-segment elevation ACS as it provides the most accurate stratification of risk both on admission and at discharge. However, there is growing interest in a more simplified approach to risk stratification [1, 3, 4]. Ranucci *et al.* introduced the Age, Creatinine and Ejection Fraction (ACEF) score, a simple, three-variable model for predicting mortality in patients undergoing elective cardiac surgery [5]. More importantly, the predictive value of the ACEF score was confirmed in different subsets of patients undergoing percutaneous coronary interventions (PCI) and transcatheter aortic valve implantation (TAVI) [6–10]. The ACEF score was associated with satisfactory predictive value not only in terms of short- and long-term mortality but also in terms of major adverse cardiovascular events, myocardial infarction, target lesion revascularization, stent thrombosis and acute kidney injury after PCI [7, 8, 10, 11]. However, the ability of the ACEF score to predict other in-hospital outcomes, including bleeding events in patients with ACS, is less established.

Aim

Thus, we aimed to assess the value of the ACEF score in prediction of death as well as other in-hospital outcomes in patients presenting with ACS in hospitals without on-site invasive facilities.

Material and methods

The Krakow Registry of Acute Coronary Syndromes was a prospective, multicenter, observational registry designed to examine in-hospital management and outcome of patients with ACS admitted to 29 community hospitals without on-site invasive facilities in this region of Poland [12–14]. Data were collected during two separate enrollment periods: from February 2005 to March 2005 and from December 2005 to January 2006, and to minimize selection bias all consecutive patients with a suspected diagnosis of ACS were included regardless of the treatment strategy or outcome. Data concerning baseline demographic and clinical characteristics, relevant laboratory results, pharmacotherapy during hospital stay and adverse cardiovascular outcomes were recorded on a standardized, electronic, web-page based case report form. Standardized definitions were used for adverse events and final diagnosis [12–14]. The decision on transfer of patients for invasive diagnostics and treatment was left to the physician's discretion.

The ACEF score was calculated using the following formula: age (years)/left ventricular ejection fraction (%) + 1 (if baseline serum creatinine was > 2 mg/dl). Direct calculation of the ACEF score was not possible in 418 (29.6%) patients due to at least one missing variable. In those patients missing data on the ACEF score were imputed using multiple imputation. Then, patients were divided into tertiles of the ACEF score.

Statistical analysis

Results are presented as numbers of patients (percentages) or medians (inter-quartile range) as applicable.

Corresponding author:
Artur Dziewierz MD, PhD, 2nd Department of Cardiology, Jagiellonian University Medical College, 17 Kopernika St, 31-501 Krakow, Poland, phone: +48 12 424 71 81, +48 12 424 71 82, fax: +48 12 424 71 84, e-mail: adziewierz@gmail.com
Received: 6.02.2017, **accepted:** 28.05.2017.

Differences in categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann-Whitney *U* test and Kruskal-Wallis test, as appropriate. Predictors of in-hospital death were identified using multivariate Cox regression analysis. Forward selection in Cox regression with the p value for covariates to enter the model were set at the 0.05 level. All variables listed in Table I

Table I. Baseline clinical characteristics

Variable	Tertiles of ACEF score			*P*-value
	1st (*n* = 471)	2nd (*n* = 472)	3rd (*n* = 471)	
Age [years]	56 (50–64)	71 (65–76)	76 (70–81)	< 0.001
≥ 75	14 (3.0%)	124 (26.3%)	245 (52.0%)	< 0.001
Male	266 (56.5%)	252 (53.4%)	266 (56.5%)	0.55
Body mass index [kg/m^2]	26.8 (24.5–30.1)	26.4 (24.2–29.4)	26.6 (24.2–29.3)	0.15
Diabetes mellitus	61 (13.0%)	97 (20.6%)	134 (28.5%)	< 0.001
Insulin	24 (5.1%)	46 (9.7%)	74 (15.7%)	< 0.001
Arterial hypertension	339 (72.0%)	378 (80.1%)	370 (78.6%)	0.007
Hyperlipidemia	285 (60.5%)	269 (57.0%)	218 (46.3%)	< 0.001
Previous angina	256 (54.4%)	335 (71.0%)	368 (78.1%)	< 0.001
Previous myocardial infarction	80 (17.0%)	142 (30.1%)	225 (47.8%)	< 0.001
Previous heart failure symptoms	18 (3.8%)	58 (12.3%)	191 (40.6%)	< 0.001
Previous percutaneous coronary intervention	36 (7.6%)	51 (10.8%)	40 (8.5%)	0.21
Previous coronary artery bypass graft	8 (1.7%)	21 (4.4%)	30 (6.4%)	0.002
Previous stroke/transient ischemic attack	13 (2.8%)	27 (5.7%)	36 (7.6%)	0.004
Current smoker	178 (37.8%)	123 (26.1%)	107 (22.7%)	< 0.001
Family history of coronary artery disease	85 (18.0%)	52 (11.0%)	64 (13.6%)	0.008
Peripheral arterial disease	19 (4.0%)	41 (8.7%)	81 (17.2%)	< 0.001
Chronic kidney disease	2 (0.4%)	3 (0.6%)	63 (13.4%)	< 0.001
Chronic obstructive pulmonary disease	20 (4.2%)	28 (5.9%)	87 (18.5%)	< 0.001
Chest pain on admission	299 (63.5%)	299 (63.3%)	308 (65.4%)	0.77
Time from chest pain onset to admission [h]	7 (3–19)	8 (3–20)	7 (3–20)	0.55
Heart rate on admission [beats/min]	75 (66–86)	80 (70–95)	80 (75–100)	< 0.001
Systolic blood pressure on admission [mm Hg]	140 (130–160)	150 (130–160)	140 (120–160)	0.003
Diastolic blood pressure on admission [mm Hg]	90 (80–100)	90 (80–100)	80 (80–100)	0.07
Cardiogenic shock on admission	8 (1.7%)	15 (3.2%)	36 (7.6%)	< 0.001
Serum creatinine level [µmol/l]	81 (70–91)	87 (70–101)	99 (80–129)	< 0.001
Left ventricular ejection fraction (%)	62 (60–68)	55 (50–60)	40 (30–48)	< 0.001
Discharge diagnosis:				
ST-segment elevation MI	97 (20.6%)	102 (21.6%)	135 (28.7%)	< 0.001
Non-ST-segment elevation MI	87 (18.5%)	114 (24.2%)	179 (38.0%)	
Unstable angina	236 (50.1%)	222 (47.0%)	141 (29.9%)	
Stable angina	26 (5.5%)	22 (4.7%)	13 (2.8%)	
Other	25 (5.3%)	12 (2.5%)	3 (0.6%)	

Values are presented as number of patients (percentage) or median (interquartile range). MI – myocardial infarction.

were tested, except for age, left ventricular ejection fraction, and baseline serum creatinine, which were included as the ACEF score. Risk of in-hospital death was expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). Receiver-operating characteristic (ROC) curve analysis was used to assess the ability of the ACEF score to predict death as well as other in-hospital events. All tests were 2-tailed, and a *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 15.0 (SPSS Inc., Chicago, Illinois).

Results

In the studied group of 1,414 patients with initial diagnosis of ACS the median ACEF score was 1.315 (1.049–1.700). A total of 471 patients had an ACEF score < 1.123 (the lowest tertile), 472 in the range 1.123–1.503 (the mid tertile), and 471 ≥ 1.504 (the highest tertile). As expected, a higher ACEF score was linked per definition with older age and more frequent chronic kidney disease. In addition, a higher ACEF score was also associated with progressively increasing clinical comorbidity; namely, diabetes mellitus, previous angina, previous myocardial infarction, previous coronary artery bypass graft, peripheral arterial disease, chronic obstructive pulmonary disease, and cardiogenic shock on admission (Table I).

Table II. Area under the curve (95% confidence interval) from receiver-operating characteristic curves of the age, creatinine, and ejection fraction (ACEF) score for in-hospital events in non-transferred patients

Parameter	AUC (95% CI)	*P*-value
Ischemic stroke	0.71 (0.55–0.86)	0.06
Major bleeding requiring blood transfusion	0.72 (0.58–0.87)	0.003
Ventricular tachycardia/ ventricular fibrillation	0.70 (0.60–0.81)	0.013
Atrial fibrillation	0.67 (0.59–0.76)	0.004
2nd to 3rd atrioventricular block	0.84 (0.78–0.90)	0.031
Pulmonary edema	0.81 (0.74–0.87)	< 0.001
Death	0.83 (0.79–0.86)	< 0.001

A total of 312 (22.1%) patients were transferred for invasive treatment during index hospital stay. The frequency of transfer for invasive treatment was the lowest in patients from the highest tertile of the ACEF score (24.6% in the lowest tertile, 25.2% in the mid tertile, and 16.3% in the highest tertile; $p = 0.001$). In the group of 1,102 patients remaining in the community hospitals for conservative treatment the median ACEF score was 1.321 (1.060–1.761) and was higher than for transferred patients: 1.282 (1.024–1.512); $p = 0.004$. Total in-hospital mortality for conservatively treated patients was 7.9%. The risk of death was higher in patients with cardiogenic shock vs. non-shock (64.4% vs. 5.5%; $p < 0.001$), as well as in ST-elevation myocardial infarction (STEMI) vs. non-ST-elevation myocardial infarction (NSTEMI) vs. unstable angina patients (22.7% vs. 12.1% vs. 1.5%; $p < 0.001$). More importantly, in-hospital mortality rates were higher in patients with a higher ACEF score (0.6% in the lowest tertile, 3.7% in the mid tertile, and 18.3% in the highest tertile; $p < 0.001$). The median ACEF score was lower in survivors than in non-survivors – 1.275 (1.035–1.658) vs. 2.089 (1.698–2.485); $p < 0.001$. In multivariate Cox regression analysis, independent predictors of in-hospital death for patients treated conservatively were: ACEF score (HR = 1.53, 95% CI: 1.27–1.85; $p < 0.001$), cardiogenic shock (HR = 6.99, 95% CI: 4.22–11.57; $p < 0.001$), chronic obstructive pulmonary disease (HR = 1.90,

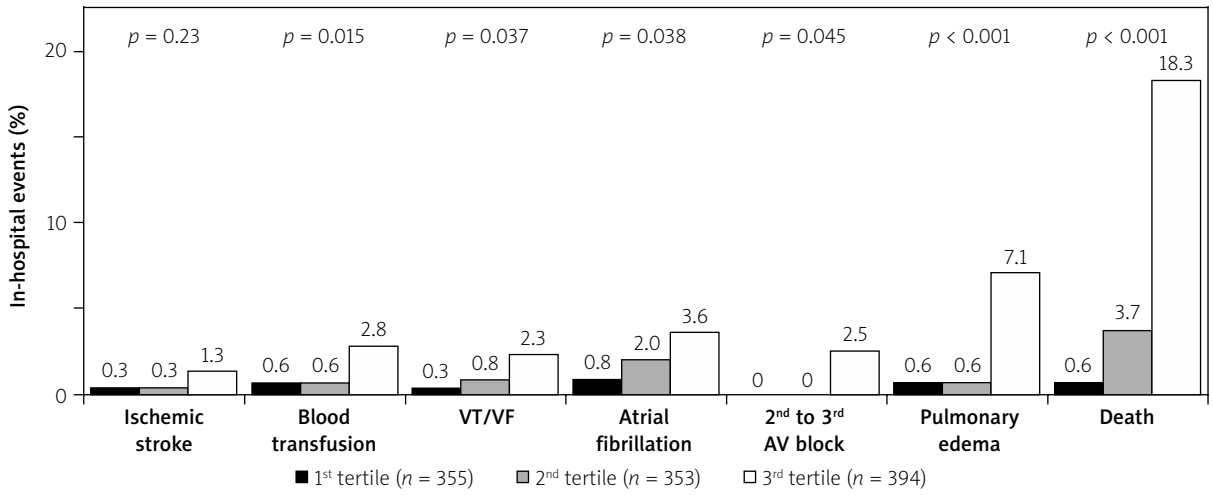

Figure 1. In-hospital complications and mortality stratified by the age, creatinine, and ejection fraction (ACEF) score tertiles in non-transferred patients

AV – atrioventricular, VT/VF – ventricular tachycardia/ventricular fibrillation.

95% CI: 1.16–3.13; p = 0.011), and STEMI (HR = 2.39, 95% CI: 1.52–3.76; p < 0.001). The ACEF score demonstrated good accuracy as a predictor of in-hospital death, as expressed by a high area under the curve (AUC = 0.83, 95% CI: 0.79–0.86; p < 0.001) – Table II and Figure 1. The predictive value was lower in the subgroup of patients with unstable angina (AUC = 0.70, 95% CI: 0.55–0.85; p = 0.06), but still satisfactory for patients with STEMI (AUC = 0.76, 95% CI: 0.69–0.83; p < 0.001) and NSTEMI (AUC = 0.81, 95% CI: 0.75–0.87; p < 0.001). As shown in Figure 1, the ACEF score was associated with increased risk of rhythm and conduction disturbances, as well as pulmonary edema and bleeding events requiring blood transfusion during the index hospital stay. In contrast, there was no difference in the frequency of ischemic stroke between study groups. The ACEF score demonstrated good accuracy as a predictor of in-hospital death as well as other outcomes (Table II).

Discussion

Our study has confirmed the ability of the ACEF score to predict not only in-hospital mortality but also other clinical events including bleeding. These findings were somewhat expected, as two of three components of the ACEF score, i.e. age and serum creatinine level, are strong predictors of ischemic and bleeding events in the setting of ACS [1, 2, 15, 16]. However, the performance of the ACEF score itself in the context of non-ischemic events in ACS, especially in patients treated conservatively during the index hospital stay, has not been previously tested. The observed AUC of 0.72 for bleeding requiring blood transfusion seems to be comparable to the values reported for other bleeding risk scores [15], but it should be confirmed in other cohorts. The ACEF score may have a limited value for the selection of patients with the highest benefit of an invasive strategy in patients with non-ST-segment ACS, as symptoms of the ongoing ischemia and/or haemodynamic instability may be more important for the decision-making process.

Several important limitations of the present study should be acknowledged. First of all, data concerning mortality in the group of patients transferred for invasive treatment during the index hospital stay, as well as long-term clinical follow-up data for all patients, were not available. Secondly, taking into account the enrollment period, the study findings may not correspond to the current clinical practice with broad access to invasive treatment and new antiplatelet and antithrombotic drugs. Thus, the study findings should be considered primarily as exploratory and hypothesis-generating. On the other hand, the findings may have some relevance for countries/regions with limited access to invasive management of ACS. Thirdly, direct calculation of the ACEF score was not possible in one third of patients. However, the results were similar in analyses conducted without multiple imputation (data not shown). Also, the performance of the ACEF score was not compared to other risk scores. Despite these limitations, the observed relationship between ACEF score and in-hospital complications and mortality of a selected cohort of conservatively treated patients with ACS is clinically important and unlikely to be influenced by the study limitations. However, these findings should be confirmed in a larger population of patients with ACS.

Conflict of interest

The authors declare no conflict of interest.

References

1. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.
2. Ando G, Costa F. Bleeding risk stratification in acute coronary syndromes. Is it still valid in the era of the radial approach? Postep Kardiol Inter 2015; 11: 170-3.
3. Filipiak KJ, Koltowski L, Grabowski M, et al. Comparison of the seven-year predictive value of six risk scores in acute coronary syndrome patients: GRACE, TIMI STEMI, TIMI NSTEMI, SIMPLE, ZWOLLE and BANACH. Kardiol Pol 2014; 72: 155-65.
4. Kiliszek M, Szpakowicz A, Filipiak KJ, et al. CHA2DS2-VASc and R2CHA2DS2-VASc scores have predictive value in patients with acute coronary syndromes. Pol Arch Med Wewn 2015; 125: 545-52.
5. Ranucci M, Castelvecchio S, Menicanti L, et al. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 2009; 119: 3053-61.
6. Capodanno D, Marcantoni C, Ministeri M, et al. Incorporating glomerular filtration rate or creatinine clearance by the modification of diet in renal disease equation or the Cockcroft-Gault equations to improve the global accuracy of the Age, Creatinine, Ejection Fraction [ACEF] score in patients undergoing percutaneous coronary intervention. Int J Cardiol 2013; 168: 396-402.
7. Biondi-Zoccai G, Romagnoli E, Castagno D, et al. Simplifying clinical risk prediction for percutaneous coronary intervention of bifurcation lesions: the case for the ACEF (age, creatinine, ejection fraction) score. EuroIntervention 2012; 8: 359-67.
8. Wykrzykowska JJ, Garg S, Onuma Y, et al. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. Circ Cardiovasc Interv 2011; 4: 47-56.
9. Zbronski K, Huczek Z, Puchta D, et al. Outcome prediction following transcatheter aortic valve implantation: multiple risk scores comparison. Cardiol J 2016; 23: 169-77.
10. Palmerini T, Caixeta A, Genereux P, et al. Comparison of clinical and angiographic prognostic risk scores in patients with acute coronary syndromes: analysis from the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial. Am Heart J 2012; 163: 383-91, 391.
11. Ando G, Morabito G, de Gregorio C, et al. The ACEF score as predictor of acute kidney injury in patients undergoing primary percutaneous coronary intervention. Int J Cardiol 2013; 168: 4386-7.

12. Dudek D, Siudak Z, Dziewierz A, et al. Local hospital networks for STEMI treatment for a population of half a million inhabitants increase the use of invasive treatment of acute coronary syndromes to the European recommended level. The Malopolska Registry of Acute Coronary Syndromes 2005-2006. Kardiol Pol 2008; 66: 489-97.
13. Dudek D, Siudak Z, Kuta M, et al. Management of myocardial infarction with ST-segment elevation in district hospitals without catheterisation laboratory--Acute Coronary Syndromes Registry of Malopolska 2002-2003. Kardiol Pol 2006; 64: 1053-60.
14. Dziewierz A, Siudak Z, Rakowski T, et al. More aggressive pharmacological treatment may improve clinical outcome in patients with non-ST-elevation acute coronary syndromes treated conservatively. Coron Artery Dis 2007; 18: 299-303.
15. Taha S, D'Ascenzo F, Moretti C, et al. Accuracy of bleeding scores for patients presenting with myocardial infarction: a meta-analysis of 9 studies and 13 759 patients. Postep Kardiol Inter 2015; 11: 182-90.
16. Watabe H, Sato A, Hoshi T, et al. Association of contrast-induced acute kidney injury with long-term cardiovascular events in acute coronary syndrome patients with chronic kidney disease undergoing emergent percutaneous coronary intervention. Int J Cardiol 2014; 174: 57-63.